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10/613,767	07/03/2003	Fu-Sheng Wang	11333/20	4833

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EXAMINER	
SCHUBERG, LAURA J	
ART UNIT	**PAPER NUMBER**
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/613,767	WANG ET AL.	
	Examiner	Art Unit	
	Laura Schuberg	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6-16 and 19-25* is/are pending in the application.

4a) Of the above claim(s) *7,8,12 and 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,9-11,13-16,19,23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3, 6-16, 19-25 are pending.

Claims 7, 8,12, 20-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected specie, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 05/18/2006.

Claims 1, 3, 6, 9-11, 13-16, 19, 23-25 have been examined on the merits.

Response to Arguments

Applicant's arguments filed 05/15/2007 have been fully considered but they are not persuasive. Applicant's arguments have been addressed in so far as they relate to the new grounds of rejection.

Applicant argues that references Sakata, Houwen, Walters and Ota do not teach or suggest generating a scattergram using settings adjusted to display a megakaryocyte population or detecting the megakaryocyte population in a predetermined megakaryocytic region of the scattergram as recited in the claimed method.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Houwen does suggest generating a scattergram and detecting a hematopoietic progenitor cell (HPC) population in a predetermined region of the scattergram (column

7) and teaches that megakaryocytes (CFU-Meg, column 8 line 1) are included as a specific subclass of HPC. Since the teachings of Sakata and Walters provide motivation and a reasonable expectation of success to substitute the Sysmex XE-2100 for the Sysmex SE-9000 used by Houwen, adjustment of the settings would have been a matter of routine optimization. In addition, Houwen provides motivation for one of ordinary skill in the art to use the Sysmex XE-2100 of Sakata for detecting megakaryocytes because Sakata suggests that the method could be used for other cell types than NRBs (p.42 column 2 and p.45 column 1) and Houwen teaches that there is a great benefit to the medical field in monitoring of megakaryocytes (column 11 lines 1-4). One of ordinary skill in the art would have adjusted the settings to ensure that the final detection of megakaryocytes (a result effective variable) was accurate and consistent with known controls. This would be a matter of quality control as well as routine optimization. The Ota reference teaches that the specific dye already used by Sakata would also be suitable for megakaryocytes as well adding to the reasonable expectation of success.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 6, 9-11, 13-16, 19, 23-25 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted

elements are: the method by which the detection is carried out, the settings required and the specific automated analyzer used. These elements are essential to carrying out the method as claimed since the method requires a detecting step, but does not indicate how this is to be carried out. The method of detection is an essential element to the claimed invention and is required for the practice of the invention. It also appears that a specific automated hematology analyzer with specific settings is required for the practice of the invention, thus making it an essential element as well.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 6, 9-11, 13-16, 19, 23-25 (old 15, 16,18, 23 and 25) are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakata (Sysmex Journal International 2000) in view of Houwen (US 5,830,701), Walters et al (Laboratory Hematology 2000), and Ota et al (Haematologia 2000).

Amended claim 1 is now drawn to a method of detecting a megakaryocyte comprising: preparing an assay sample by combining a sample comprising a cell with a reagent comprising a fluorescent dye, wherein the preparing does not involve an immunological method; detecting a plurality of morphological information; generating a scattergram using settings adjusted to display a megakaryocyte population; and detecting the megakaryocyte if a population exists in a predetermined megakaryocyte region of the scattergram.

Claim 3 is drawn to wherein the detecting involves an automated hematology analyzer.

Claim 6 is drawn to wherein the plurality of morphological information comprises side scattered light and fluorescent light emitted by the cell.

Claim 9 is drawn to wherein the detecting comprises passing the assay sample through an electrically charged aperture and identifying a change in direct current resistance and radio frequency resistance.

Claim 10 is drawn to identifying the megakaryocyte region of the scattergram.

Amended claim 15 is now drawn to a method of detecting a megakaryocyte comprising: preparing an assay sample by combining a sample comprising a cell with a reagent comprising a fluorescent dye, wherein the preparing does not involve an immunological method; detecting a plurality of information from the cell, wherein the information is selected from the group consisting of cell size, cell interior, degree of cell staining and combinations thereof; generating a scattergram by plotting the plurality of information using settings adjusted to display a megakaryocytic population; and detecting the megakaryocyte if a population exists in a predetermined megakaryocyte region of the scattergram. (Applicant has elected the combination of cell interior information and degree of cell staining information as the species of cell information.)

Claim 16 is drawn to wherein the detecting involves an automated hematology analyzer.

Amended claim 19 is drawn to wherein the cell interior information is based on side scattered light emitted by the cell, and the degree of cell staining information is detected based on fluorescent light emitted by the cell.

Amended claim 23 is now drawn to a method of detecting a megakaryocyte comprising preparing an assay sample by combining a sample comprising a cell with a reagent comprising a fluorescent dye and a hemolytic agent, wherein the preparing

does not involve an immunological method; detecting scattered light and fluorescent light emitted by the cell; generating a scattergram by plotting the scattered and the fluorescent light using settings adjusted to display a megakaryocytic population; detecting the megakaryocyte if a population exists in a predetermined megakaryocyte region of the scattergram.

Claim 24 is drawn to wherein the scattered light comprises side scattered light.

Claim 25 is drawn to wherein the detecting involves an automated hematology analyzer.

Sakata teaches a method of detecting nucleated red blood cells (NRBC) with a reagent that comprises a fluorescent dye (polymethine) and a hemolytic agent (p.41). Scattered light and fluorescent light are detected and a scattergram is generated (p.44). The detecting involves an automated hematology analyzer (XE-2100) (p.41). The preparing of the sample does not involve an immunological method. In addition, Sakata teaches that in the Xe-2100, by developing and using optimum polymethine dyes not only for the NRBC channel, but also the 4 DIFF and RET channels, a wide variety of normal and abnormal cells can be classified and counted (p.42 column 2). Sakata also teaches that the automated hematology counter will be able to count all types of cells-including, in the future, cells presently considered to be "impossible" to count (p.45).

Sakata does not teach the use of the method to detect megakaryocytes or to determine if a population exists in a megakaryocyte region of a scattergram.

Houwen teaches the use of the automated hematology analyzer, SE-9000 (column7 line 51), for the detection of megakaryocytes (column 4 line 35) and for the

determining of the region of the scattergram where the megakaryocyte population exists (column 7 lines 53-55). The use of a flow cytometer operating on an optical principle is taught as an alternative particle analyzer (column 7 line 17). Houwen also teaches that there is a great benefit to the medical field in monitoring of hematopoietic progenitor cells (which includes megakaryocytes) in peripheral blood stem cell transplantation (column 11 lines 1-4). Where the detecting comprises passing the assay through an electrically charged aperture and identifying a change in direct current (DC) resistance and radio frequency (RF) resistance is taught as well as cell size information based on a change in DC and cell interior information based on a change in RF (column 7 lines 2-23)(claim 9). Houwen teaches obtaining cell information about the treated blood sample using a particle analyzer and constructing a cell distribution profile (scattergram); delineating a portion of the profile as a zone in which at least one subclass of hematopoietic progenitor cells appear; wherein the profile zone is delineated through the use of a control sample comprising hematopoietic progenitor cells and counting the cells in the zone (column 11). Examples of the cell interior information include lateral (side) scattered light (column 7 lines 7-10).

Walters teaches that a comparison between hematology analyzers Sysmex XE-2100 and Sysmex SE-9000 showed excellent correlation for all parameters except number of basophils (p.89). Walters also teaches that the Sysmex XE-2100 has proven to be an accurate and precise high-speed analyzer and is suitable for both high volume laboratories and laboratories that test many abnormal samples (p.92).

Ota teaches that violet polymethine dye (VPM) is a megakaryocyte-specific stain that is clinically useful for estimating of megakaryocyte count, classification of megakaryocytes and identification of immature megakaryocytic cells (p.21).

One of ordinary skill in the art would have been motivated to use the method of Sakata for the detection of megakaryocytes because Sakata suggests that the method could be used for other cell types than NRBs (p.42 column 2 and p.45 column 1) and Houwen teaches that there is a great benefit to the medical field in monitoring of megakaryocytes (column 11 lines 1-4). One of ordinary skill in the art would have been motivated to identify a megakaryocytic region in the scattergram generated by the method of Sakata because regions for other cell types are also generated upon detection. One of ordinary skill in the art would have been motivated to use side-scattered light when detecting megakaryocytes because Houwen teaches that this type of cell interior information is useful for detecting megakaryocytes. Using settings adjusted to display a megakaryocyte population would have been a matter of routine optimization since the artisan of ordinary skill would recognize that the results would depend upon optimal settings of the hematology analyzer and comparison with manual and flow cytometry results would have allowed reference controls to ensure accuracy. One of ordinary skill in the art would have had a reasonable expectation of success because Walters teaches that the Sysmex XE-2100 (used by Sakata) showed excellent correlation with the Sysmex SE-9000 (used by Houwen to detect megakaryocytes) and Ota teaches that a polymethine dye (also used by Sakata with the Sysmex XE-2100) is specific for megakaryocytes allowing detection of megakaryocytes as well.

Therefore, the combined teachings of Sakata, Houwen, Walters, and Ota render obvious Applicant's invention as claimed.

Claims 11, 13, 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakata (Sysmex Journal International 2000) in view of Houwen (US 5,830,701), Walters et al (Laboratory Hematology 2000), and Ota et al (Haematologia 2000) as applied to claims 1, 3, 6, 9, 10, 15, 16, 19, 23-25 above, and further in view of Tomer et al (Blood 1988).

Claim 11 is drawn to claim 10 wherein the identifying comprises 2 reference scattergrams, one with purified megakaryocytes and one substantially free of megakaryocytes and comparing them.

Claims 13 and 14 are drawn to claim 11 wherein the purified megakaryocyte comprises a cell induced from a CD34 positive hematopoietic cell by thrombopoietin.

Tomer teaches a method of detecting megakaryocytes that includes preparing an assay sample by combining bone marrow from normal human donors (p.1244 column 2) with fluorescent antibodies (dye) and a hemolytic agent (0.1% sodium citrate) (p.1245 column 1). Data collection of the fluorescence intensities and scattered light of each cell are carried out (p.1245 column). Scattergrams are generated by plotting scattered light and fluorescent light (p.1246 column 1). A megakaryocytic region is identified in the scattergrams by generating 2 reference scattergrams, one with purified megakaryocytes

and the other without (p.1246 column 1). A population is determined to exist in a megakaryocytic region of the scattergram. The cell interior information is detected based on side-scattered light and the degree of cell staining information is detected based on fluorescent light emitted by the cell (p.1244 column 2). An automated hematology analyzer is also taught (p.1244 column 2).

Since Houwen teaches that the appearance zone of megakaryocytes is delineated based on the scattergram pattern for the appearance of megakaryocytes, one of ordinary skill in the art would have been motivated to include a reference scattergram without megakaryocytes as a negative control to improve the accuracy of the final result. One of ordinary skill in the art would have been motivated and had a reasonable expectation of success because Tomer was using such a negative control to identify a megakaryocyte region on a scattergram as well.

The purified megakaryocytes are inherently induced from CD34 positive hematopoietic cells by thrombopoietin (TPO) and this induction occurs *in vivo*. Since the claim language does not require the induction to be *in vitro*, this meets the limitations of claims 13 and 14 as claimed.

Therefore, the combined teachings of Sakata, Houwen, Walters, Ota, and Tomer render obvious Applicant's invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura Schuberg whose telephone number is 571-272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leon B Lankford, Jr
Primary Examiner
Art Unit 1651

Laura Schuberg